Public Health Ontario | Santé publique Ontario

SYNTHESIS

Acute Severe Hepatitis of Unknown Origin among Young Children – What We Know So Far

Published: June 2022

Introduction

Public Health Ontario (PHO) is actively monitoring, reviewing and assessing relevant information related to cases of acute severe hepatitis of unknown origin among young children. "What We Know So Far" documents provide a rapid review of the evidence related to this issue.

Key Findings

- As of May 30, 2022, the World Health Organization (WHO) has reported more than 650 cases of acute severe hepatitis with an unknown etiology in children since Oct 2021, primarily from the United Kingdom (UK) and United States (US). As of May 20, 2022, the Public Health Agency of Canada (PHAC) has reported ten cases in Canada, including four in Ontario. We note that case definitions used for case ascertainment are very broad, likely producing a highly heterogeneous group and variable case counts among jurisdictions.

- Whether there has been an increase in acute severe hepatitis of unknown etiology remains unclear, as observed case counts do not exceed expected case counts in many countries. Studies on the etiology of acute severe hepatitis in children and pediatric acute liver failure (PALF) fail to determine an etiology in about 30%–50% of all cases

- The majority of cases reported to date have been among those <5 years of age; however, there is no observed difference in incidence according to patient sex, racial background or geography.

- Signs and symptoms reported in children with acute severe hepatitis of unknown etiology include jaundice, vomiting, diarrhea, pale stool, fever, lethargy and abdominal pain, in conjunction with elevated liver enzymes (aspartate transaminase [AST] or alanine transaminase [ALT] > 500 IU/L). Worldwide, approximately 6% of children required a liver transplant and nine children have died.

- Currently, there are two leading hypotheses for the potential increase in acute severe hepatitis of unknown etiology in children, based on epidemiological investigations and laboratory testing; however, the cause remains unknown and other causes continue to be explored.

Adenovirus:

- One hypothesis is that an unidentified cofactor in children with adenovirus infection is triggering a more severe adenovirus infection (which would normally be mild) or is causing immune-mediated damage to the liver. In addition, the cause could be a novel adenovirus or strain, co-infection with another pathogen, and/or infection worsened because of a naive immune system.

- Infection with adenovirus is common in children and detected by polymerase chain reaction (PCR) in asymptomatic children due to viral persistence and/or shedding; however, PCR positivity alone cannot be used to attribute causation.

- Investigators have detected adenovirus in some, but not all children with acute severe hepatitis. In cases with liver biopsies, the biopsies have not demonstrated viral inclusions, immunohistochemical evidence of adenovirus or viral particles –questioning the hypothesis that adenovirus is a direct cause of hepatitis.

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2):

- Liver involvement is uncommon in children with SARS-CoV-2 infection, but investigators have noted SARS-CoV-2 liver tropism in adults.

- SARS-CoV-2 testing is often negative at the time of hepatitis presentation. When investigators perform SARS-CoV-2 serology, there is often evidence of prior infection; however, use of SARS-CoV-2 serology was inconsistent and the significance is unclear when seroprevalence is high.

- A post-infectious process is considered a possible explanation, given inflammatory conditions (specifically that multisystem inflammatory syndrome in children [MIS-C]) have been associated with SARS-CoV-2.

- Other possible explanations for the current trend in acute severe hepatitis in children include possible toxin exposure, drug toxicity or an undescribed novel pathogen; currently, investigations are underway to determine if these are possible causes.

- The illness is not associated with Coronavirus Disease 2019 (COVID-19) vaccination, as most of the affected children had never received, or were ineligible for, a COVID-19 vaccine.

Background

On Apr 5, 2022, WHO was notified by the UK that there were 10 pediatric patients (age range: 11 months–5 years) hospitalized for acute severe hepatitis (non-hepatitis virus A-E) of unknown etiology.[1] Initial reported cases were located across central Scotland with onset dates from Jan through Mar 2022.[2] For reference, typically less than four cases occur annually in Scotland.[3] As of May 27, 2022, the WHO reported 650 cases of acute severe hepatitis with unknown etiology in children ≤16 years since Oct 1, 2021, with the majority of cases reported from the UK and US.[4] On May 20, 2022, PHAC confirmed 10 cases of acute severe hepatitis in children of unknown etiology in Canada (meeting the national case definition, Appendix A).[5] The cases were reported from Ontario (n=4), Alberta (3), Manitoba (2) and Quebec (1), with illness onset dates ranging from Nov 3, 2021 through Apr 23, 2022.

Public health investigations of cases in affected countries include investigation of exposure history, toxicology, virology and microbiology testing. Spatial and temporal linkages between identified cases are being explored in addition to genetic characterization of pathogens in those individuals who have tested positive for SARS-CoV 2, adenovirus and/or other pathogens. According to the WHO, while adenovirus has been detected in many cases, this does not explain the severity of illness observed, particularly as most cases were reported to be previously healthy.[2]

The purpose of this document is to summarize the information and literature available to date regarding cases of severe acute hepatitis of unknown etiology in children, including etiology hypotheses.

Methods

In considering feasibility, scope, and a need for responsiveness, we chose a rapid review as an appropriate approach to understanding acute severe hepatitis in children (with unknown etiology). A rapid review is a knowledge synthesis where certain steps of the systematic review process are omitted (e.g., duplicate screening, quality assessment) in order to be timely.

PHO Library Services conducted literature searches in MEDLINE (May 2, 2022), National Institutes of Health COVID-19 Portfolio (Preprints) (Apr 29, 2022), Embase (May 2, 2022) and Global Health/Scopus (May 2, 2022). Literature search strategies are available upon request. We searched PubMed on May 31, 2022 for additional articles of interest.

English-language peer-reviewed and non-peer-reviewed studies that described the etiology of acute severe hepatitis in children or PALF were included. This rapid review concentrated on evidence from systematic reviews and meta-analyses, supplemented by primary literature where appropriate. This synthesis does not address the management of children with acute severe hepatitis. In addition, for the purpose of this review, we concentrate on studies from developed countries.

Prior to posting, PHO subject-matter experts review all knowledge products. The increase in acute hepatitis cases in children will continue to evolve and the scientific evidence will rapidly expand; therefore, the information provided in this document is only current as of the date of the respective literature searches.

Here we present a summary of relevant literature pertaining to current hypotheses[3] regarding the observed increase of acute severe hepatitis of unknown origin among young children.

Results

Clinical Manifestations, Laboratory Results and Disease Severity

Clinical presentation of cases includes jaundice, in some cases preceded by gastrointestinal symptoms (predominantly vomiting) and/or diarrhea and/or abdominal pain in conjunction with elevated liver enzymes (ALT or AST > 500 IU/L).[2] For jurisdiction-specific case definitions for acute severe hepatitis of unknown origin among young children, please refer to Appendix A.

- In a study of nine children with acute severe hepatitis in Alabama, US (symptom onset Oct 2021 to Feb 2022), Baker et al. (2022) reported that the most common presenting symptom was vomiting (7/9).[6] Other presenting symptoms included diarrhea (6/9), fever (5/9) and upper respiratory symptoms (3/9). The authors noted that upper respiratory symptoms included nasal congestion, nasal discharge, cough, sore throat, wheezing and dyspnea. Physical examination noted scleral icterus in 8/9 children, followed by hepatomegaly (7/9), jaundice (6/9), hepatic encephalopathy (1/9) and splenomegaly (1/9). Laboratory findings noted elevated ALT (range: 603–4,696 U/L), AST (range: 447–4,000 U/L) and total bilirubin (range: 0.2–13.5 mg/dL). The International Normalized Ratio (INR) was not determined. All children required hospitalization and three required a liver transplant. The age of patients ranged from 0 to 6 years, with 5/9 children <2 years. The authors included any child with acute hepatitis with a positive adenovirus test (and no other identifiable etiology).

- In an initial investigation into the clinical and epidemiological data from the 13 cases reported as part of the initial cluster in Scotland (symptom onset Jan 1 to Apr 12, 2022), Marsh et al. (2022) reported that the most common symptom at presentation was jaundice (9/9 patients for which symptoms were reported). Additional symptoms included abdominal pain (7/9), nausea (6/9) and malaise (6/9).[3] The authors noted that most of the patients had elevated ALT and AST (i.e., >2,000 IU/L); the INR was not determined. All cases required hospitalization (for at least 6 days) and one child required a liver transplant. The median age of the children was 3.9 years (interquartile range [IQR]: 3.6–4.6). The authors defined a confirmed cases as children ≤10 years with elevated transaminases (>500 IU/L) since Jan 1, 2022, or contact with a confirmed or possible case. A possible case was a child ≤10 years with jaundice of unknown cause since Jan 1, 2022, or contact with a confirmed or possible case.

- In a study of acute severe hepatitis and pediatric acute liver failure (PALF) in children from 34 pediatric liver centres in Europe and Israel (symptom onset Jan 1 to Apr 26, 2022), de Kleine et al. (2022) reported on 64 children with acute severe hepatitis or PALF.[7] The mean age of children was 7.7 years (range: 1 month–16 years). All children were hospitalized and four required a liver transplant; three children died. Children showed elevated ALT (mean: 2,871 IU/L) and INR (mean: 3.0). Acute severe hepatitis cases included all children ≤16 years since Jan 1, 2022 presenting with elevated aminotransferases (>500 IU/L) and negative for hepatitis virus A-E. PALF included children with acute hepatic injury (elevated ALT), a spontaneous INR ≥ 2.0 or INR ≥ 1.5 with signs of hepatic encephalopathy.

- As of May 19, 2022, the UK Health Security Agency (UKHSA) reported 197 cases of acute severe hepatitis in children.[8] The most commonly reported symptom was jaundice (68.8%, 99/144), followed by vomiting (57.6%), lethargy (48.6%), diarrhea (43.1%), pale stools (42.7%), abdominal pain (36.1%), fever (28.5%), nausea (25.7%) and respiratory symptoms (18.1%). For cases with available information (n=181), all but one case was hospitalized; 11 cases required liver transplantation.

- As of May 20, 2022, PHAC has reported that all 10 confirmed cases of acute severe hepatitis in children in Canada required hospitalization and two required a liver transplant.[5] Please note that the case definition requires hospitalization (Appendix A).

- Worldwide, as of May 27, 2022, the WHO reported that admission to an intensive care unit was required in 14.1% (22/156) of cases.[34] Thirty-eight children required a liver transplant and nine children died.

Incidence

Currently, is not clear if the current incidence of acute severe hepatitis with no apparent etiology in children is above expected values. Clinicians at major pediatric liver centers in the Netherlands and Denmark have reported increases in the number of children referred for liver transplantation, with the number of those assessed in the first four months of 2022 being similar to that typically seen in a full year. Similarly, hospital clinicians in Denmark have reported an increase in the number of pediatric cases with acute liver failure.[9]

- In a study of acute severe hepatitis in children from 24 countries (symptom onset Jan 1 to Apr 18, 2022), van Beek et al. (2022) reported that 5/17 European counties and 1/7 non-European countries had an increase in probable cases compared to the previous five years (see article for case definition). Severe cases of acute hepatitis increased in five countries (i.e., Italy, Poland, Spain, Sweden, UK).[10]

- In a study of acute severe hepatitis and PALF in children from 34 pediatric liver centres in Europe and Israel (symptom onset Jan 1 to Apr 26, 2022), de Kleine et al. (2022) reported that 22 centres did not report an increase in acute severe hepatitis and PALF (see previous for case definitions used; conditions not separated in results).[7] Twelve centres reported a suspected increase in cases; however, documentation of this increase was not provided (authors do not report which countries these are). In 11 transplant centres with ≥16 paediatric liver transplantations per year, there was a reported a mean of 2.5 cases (range: 0–5) in 2022, compared to mean cases per year in 2019 (mean: 4.9, range: 0–10), 2020 (mean: 3.7, range: 0–10) and 2021 (mean: 4.9, range: 0–10).

Etiology Hypotheses

Infectious disease agents, autoimmune conditions, metabolic disorders and toxins cause acute severe hepatitis in children.[11] Here we provide a brief overview of various causes of acute severe hepatitis in children that are currently being explored as potential explanations for the apparent observed increase in cases worldwide. With this in mind, we will concentrate on adenovirus and SARS-CoV-2 infections (or combinations of both) as the leading etiology hypotheses.

The primary hypotheses for the etiology of acute severe hepatitis in children are:

- Adenovirus infection (e.g., a novel adenovirus strain, co-infection with or priming by another pathogen, large wave of infection leading to more frequent detection of uncommon outcomes and/or infection worsened because of a naive immune system)

- A new SARS-CoV-2 variant of concern (VOC) or undescribed sign or symptom of a recently emerged VOC (i.e., Omicron)

- A post-acute SARS-CoV-2 infection syndrome (similar to multisystem inflammatory syndrome in children, MIS-C) or sequelae from SARS-CoV-2 infection

- A non-infectious cause (e.g., toxin or drug)

- A novel pathogen not detectable with current diagnostics

In studies of PALF, the proportion of cases that have an unknown etiology typically range from 31% to 53%. Unless otherwise stated, PALF includes children with 1) acute onset of liver disease;2) no known underlying chronic liver disease; 3) biochemical evidence of severe liver injury; and 4) coagulopathy not corrected by vitamin K and INR ≥ 1.5 or prothrombin time (PT) ≥ 15 seconds in patients with encephalopathy or an INR ≥ 2.0 or PT ≥ 20 seconds in patients without encephalopathy. Aside from unknown causes, the most commonly reported causes of PALF in children from developed nations were acetaminophen toxicity, metabolic disorders, autoimmune disorders and infectious agents.

- In a systematic review and meta-analysis of 32 studies and 2,019 children with PALF in developed countries, Berardi et al. (2020) reported that the most common etiology was acetaminophen toxicity (mean: 9.2%, 95% confidence interval [CI]: 7.99–10.6), followed by other etiologies such as unspecified metabolic disorders (5.5%, 95% CI: 4.50–6.52) and infectious agents (5.1%, 95% CI: 4.13–6.08).[12] A cause of hepatitis was not found in 39.7% (95% CI: 37.6–41.9) of children. The age of included children was 0–22 years.

- The Pediatric Acute Liver Failure Study Group in Canada, UK and US reported on the etiology of PALF in 1,114 children from 1994 through 2014.[11] 42.9% of cases had an unknown etiology (approximately 59% in children 3 months to 3 years), followed by other etiologies such as acetaminophen toxicity (13.3%), unspecified viral causes (8.4%) and autoimmune disorders (6.6%). The authors noted another study demonstrating that children with acute hepatitis of unknown origin often have $CD8^+$ T-cell infiltrate in liver biopsies, leading to a hypothesis that liver injury is due to immune dysregulation and a hyper-inflammatory response (Chapin et al. 2018, Chapin et al. 2020).[13,14]

- In a retrospective study of acute liver injury among 785 children in Italy and the Netherlands (2000–2008), Ferrajolo et al. (2013) noted that 50% of acute liver injury cases were idiopathic. Additional causes included drug toxicity (e.g., antibiotics, 15%) and other causes such as autoimmune disorders, metabolic disorders and infections (<10% each).[15] The mean age of children with no known cause for their acute liver injury was 12 years.

- Using the Pediatric Health Information System database in the US, Kulkarni et al. (2015) reported on 583 cases of PALF (2008–2013).[16] In 52.5% of patients, an etiology was not determined and acetaminophen toxicity was the cause in 18.7% of cases, followed by viral infections (6.5%). Among 38 patients with a viral etiology, the most commonly detected virus was Epstein-Barr virus (EBV, 18.4%), followed by adenovirus (13.3%), cytomegalovirus (CMV, 10.5%), hepatitis A virus (HAV, 5.3%) and parvovirus (2.6%); 47.3% of cases did not have a specific virus reported. The mean age of children was 9.4 ± 5.6 years.

- In a study of 348 children (<18 years) with PALF in Texas, US, Squires et al. (2006) reported that 49% of cases were idiopathic, followed by 14% caused by acetaminophen toxicity, 10% from metabolic diseases (e.g., Wilson disease, respiratory chain defect, mitochondrial disorder), 6% from autoimmune conditions and 6% from infectious agents (e.g., EBV, adenovirus, herpes simplex virus).[17]

- In Australia, the etiology of PALF in 58 children was unknown in 31% of cases; the most common etiology being metabolic disorder (26%), followed by infectious agents (15%), drug-induced liver failure (13%), hemophagocytic lymphohistiocytosis (9%) and autoimmune disorder (6%).[18] The median age of patients was 17 months (range: 1 day–15.6 years).

- In a retrospective review of 34 children with PALF in Singapore from 2007–2019, Chiou et al. (2021) reported that the cause of PALF was indeterminate in 41.2% of cases, or due to metabolic (26.5%) or infectious causes (26.5%).[19] Etiology differed by age, with metabolic disorders being more common among children <12 months, and an indeterminate cause being more common in children aged ≥1 year.

Other causes of acute severe hepatitis or PALF in children in developed countries include herpsesvirus-6 infection (w/ mutation in neuroblastoma-amplified gene protein),[20] echovirus 25,[21] CMV,[22,23] Wilson disease,[24] human bocavirus infection (w/ T-cell deficiency),[25] parvovirus B19,[26,27] influenza A virus,[28,29] mushroom ingestion[30] and exposure to algal blooms.[31] Of note, the current working case definition in Canada excludes cases of hepatitis due to genetic, congenital, metabolic, oncologic, vascular- or ischemia-related conditions, in addition to those caused by or attributed to a known or expected presentation from a drug or medication, or from an acute worsening of chronic hepatitis (Appendix A).[32] Preliminary investigations in the UK have not identified any evidence of toxicity associated with paracetamol or aflatoxin, and detailed toxicological investigations for organic compounds and metals have not identified any significant findings.

ADENOVIRUS

Human adenoviruses (HAdVs) are classified into one of seven serogroups (designated A-G), with over 100 genotypes and 52 serotypes of HAdV being identified worldwide (Lynch and Kajon 2021).[33] Predominant serotypes vary by country and change over time. There is different tissue tropism between serotypes, accounting for the different clinical syndrome typically associated with certain serotypes. While HAdVs typically cause mild respiratory infection or gastrointestinal infection, and are more common among children due to lack of immunity, in rare cases dissemination of infection and extrapulmonary manifestations of illness may occur, including hepatitis, pancreatitis and nephritis (Lynch and Kajon 2021).[33] Both the Netherlands and the UK have reported increased levels of HAdVs in the community compared to earlier in the pandemic.[2] Scotland reported that community levels of HAdVs in Mar 2022 were comparable to pre-pandemic levels.[3]

Several recent studies of acute severe hepatitis in children have detected HAdVs during testing.

- In a study of acute severe hepatitis in children from 34 pediatric liver centres in Europe and Israel (symptom onset Jan 1 to Apr 26, 2022), de Kleine et al. (2022) reported on 13 of 64 children with severe hepatitis or PALF who underwent viral testing. Four of the 13 children tested positive for HAdVs (no documentation of specimen type or serotype).[7] The mean age of children was 7.7 years (range: 1 month–16 years).

- In a study of 13 cases of acute severe hepatitis in Scotland, five of the children were positive for HAdVs by PCR on respiratory swab, stool and whole blood (Marsh et al. 2022).[3] Of these five children, three were also PCR positive (n=2) or historically PCR positive (n=1; >3 months prior to presentation) for SARS-CoV-2. An additional two children who tested negative for HAdV were PCR positive (n=1) or historically PCR positive (n=1; >3 months prior to presentation) for SARS-CoV-2. The median age of the 13 children was 3.9 years. Adenovirus case counts in Scotland in Mar 2022 were comparable to pre-pandemic peaks, however the number of children <5 years presenting with abnormal liver function testing in Mar 2022 were higher than expected compared to the same time period in the previous 3 years.

- In a cluster investigation of nine children with acute severe hepatitis in Alabama, US (symptom onset Oct 2021 to Feb 2022), Baker et al. (2022) reported that all children tested positive for adenovirus.[6] Two of four cases with typing information were HAdV F Type 41.

- The UKHSA (May 19, 2022) reported that 64.8% (116/179) of patients with acute severe hepatitis tested positive for adenovirus through PCR (mostly on whole blood).[8] As of May 27, 2022, in the UK, the WHO reported that for adenovirus-positive cases with typing results, 27 of the 35 cases were Type 41.[4] However, in a May 31, 2022 joint report by WHO and European Centre for Disease Prevention and Control (ECDC) only four typing results were available, in which two were Type 41.[34]

- Brodin and Arditi (2022) hypothesized that the cause of the current acute severe hepatitis in children is a HAdV infection with gastrointestinal trophism preceded by SARS-CoV-2 infection.[35] Specifically, SARS-CoV-2 persistence in the gastrointestinal track and immune response leads to non-specific T-cell activation and IFN-ϒ upregulation and damage to hepatocytes.

Historically, acute severe hepatitis is uncommon as a clinical manifestation of HAdV infections.

- In a review of the clinical manifestation and pathology of human adenoviruses in children, Shieh (2021) noted that there are 104 different types of HAdV, with most of these belonging to species D (73 types), of which HAdV D Type 41 is a common cause of gastroenteritis in children, particularly in North America and Southern China.[36] Tissue tropism varies among adenoviruses, and although HAdVs most commonly cause respiratory infection in children, these have also been associated with disease in other body systems; e.g., HAdV Type 41 has been associated with gastroenteritis and HAdV Types 1, 2, 3, 5 and 7 have been associated with hepatitis. The author notes that there were few documented cases of HAdV-associated hepatitis in immune competent pediatric patients.

- In a study from China examining the molecular and epidemiological characteristics of HAdV infections in children <5 years, who presented with acute diarrhea from 2017 through 2018, HAdV was detected in 7.5% of stool specimens, with the average age among children testing positive being 17.9 months (Huang et al. 2021).[37] A seasonal pattern of infection was observed, with higher rates of infection during the winter months of Dec–Feb. HAdV 41 (species F) was the most common serotype detected, and the highest positivity rate was observed in children aged 13–24 months.

- A surveillance study of HAdV-F genotypes was conducted in eastern India from 2017–2020 to analyze the evolution of this genotype, a leading cause of pediatric gastroenteritis, based on an observed shift from HAdV-F41 being the most prevalent in 2007–2009, to HAdV-F40 predominating in 2013–2014 (Chandra et al. 2021).[38] Via PCR testing of stool specimens collected from children aged ≤5 years, the authors noted an enteric HAdV prevalence of 9.0%, with children <2 years being most vulnerable to infection. HAdV-F41 strains mutated over the study period, while HAdV-F40 strains exhibited genetic conservation.

- In a case-control study comparing the epidemiology and clinical characteristics of pediatric cases of pneumonia caused by SARS-CoV-2, influenza A virus and HAdVs, Liu et al. (2022) found that a cough, fever and wheezing occurred more commonly in patients who were infected with influenza A or HAdV compared to those with SARS-CoV-2.[39]

- A cross-sectional study, examining the symptomatology and epidemiology of respiratory HAdV infections in China, found that HAdV was detected in 6.9% of pediatric inpatients who were diagnosed with an acute respiratory infection, with most cases occurring during the winter (Wang et al. 2021).[40] The highest rate of detection was in children aged 6–24 months. Predominant symptoms among those testing positive for HAdVs included a fever (93%), cough (95%), wheezing (26%) and shortness of breath (15%); 28% of cases had extrapulmonary symptoms, including hepatic injury (6.4%) and myocardial injury (3.5%). Co-infections with one or more respiratory pathogens occurred in over 40% of patients with HAdV (43.6%), with the most commonly co-detected pathogens being influenza virus (24.4%), parainfluenza virus (18.8%) and RSV (13.6%).

- A surveillance study in Amman, Jordan (2010–2013) detected HAdV in 15% of children hospitalized with an acute respiratory infection, with HAdV-C being the most common serotype detected among those with typology available (140/215; 65%) (Probst et al. 2022).[41] Symptomatology differed between children infected with only HAdV compared to children co-infected with HAdV and other viruses, with those infected with two or more viruses being more likely to require oxygen support. Co-infection was more common in those with HAdV-C compared to those with HAdV-B.

- An outbreak of HAdV Type 7 occurred among 14 children hospitalized in a pediatric ward in Japan from Nov 1996 to Jan 1997 (Sakata et a. 1998).[42] The age of children ranged from 2 months to 5 years. All children had pneumonia, while nine had gastroenteritis and three had liver dysfunction.

- In a case report of a previously healthy 18-month-old child in Turkey, Özbay Hoşnut et al. (2008) reported that the child presented at the hospital with diarrhea, vomiting and jaundice. The child's condition deteriorated to coma, with abnormal coagulation tests, elevated total bilirubin (50 mg/dL), AST (149 IU/L), ALT (193 IU/L), INR (3.8) and liver failure (no hepatomegaly).[43] Serology was positive for adenovirus IgM and IgG; however, liver biopsy upon autopsy was negative for HAdV antigens using immunohistochemistry and PCR.

- Matoq and Salahuddin (2016) reported on a previously healthy 23-month-old child with hepatitis in Florida, US. Prior to presentation, the child experienced vomiting, diarrhea, cough, rhinorrhea, fever, lethargy and swelling of the extremities.[44] Upon testing, the child had elevated AST (889 IU/L), ALT (740 IU/L) and INR (1.5) with evidence of pancytopenia and a positive test for HAdV (nasopharyngeal swab [NP] by RT-PCR).

SARS-COV-2

Currently, it remains unknown whether acute SARS-CoV-2 infection or previous SARS-CoV-2 infection in children may lead to hepatitis. The current evidence notes that liver involvement is uncommon in children with SARS-CoV-2 infection or exposure. In contrast, there is some evidence that multisystem inflammatory syndrome in children (MIS-C) could lead to hepatitis; suggesting that a similar mechanism responsible for MIS-C is producing a similar hepatic-gastrointestinal syndrome. MIS-C is an uncommon systemic inflammatory vasculopathy of children that can occur following SARS-CoV-2 infection.

Several recent studies involving acute cases of hepatitis in children have detected SARS-CoV-2 during testing.

- In a study of acute severe hepatitis in children and PALF from 34 pediatric liver centres in Europe and Israel (symptom onset Jan 1 to Apr 26, 2022), de Kleine et al. (2022) reported on 13 children with viral testing, in which four tested positive for SARS-CoV-2 (testing not specified).

- Among 13 severe acute hepatitis cases reported in Scotland, five of the children were positive for SARS-CoV-2 by PCR (current tests or historical tests);[3] three of these also had adenovirus co-detection or co-infection. Dates of positive adenovirus and SARS-CoV-2 tests ranged from Dec 29, 2021 through Apr 4, 2022, while the dates of symptom onset ranged from Mar 4 to Apr 7, 2022. There was no clear pattern in appearance of symptoms and testing positivity: Case 2 (presentation: Mar 5, adenovirus positive: not applicable [NA], SARS-CoV-2 positive: Mar 17), Case 5 (Mar 21, Mar 22, Dec 29), Case 7 (Mar 24, Apr 4, NA), Case 8 (Mar 26, Mar 26, Mar 28), Case 9 (Mar 28, Mar 30, Mar 30), Case 10 (Mar 30, Dec 29, NA) and Case 11 (Mar 31, NA, Apr 1).

- In a study of nine children with acute hepatitis in Alabama, USA (symptom onset Oct 2021 to Feb 2022), Baker et al. (2022) reported that none of the children tested positive by PCR for SARS-CoV-2 infection at the time of presentation with acute hepatitis.[6] However, prior SARS-CoV-2 infection cannot be ruled out since SARS-CoV-2 serology was not performed.

- The UKHSA (May 19, 2022) reported that 12.8% (16/125) of patients with acute severe hepatitis had a current or previous positive PCR result for SARS-CoV-2.[8] Thirteen patients tested positive for SARS-CoV-2 upon hospital admission, while three tested positive in the eight weeks before admission.

- In the European Region, as of May 27, 2022, the WHO reported that among 188 cases of acute severe hepatitis, 12.2% (23/188) of children had a positive SARS-CoV-2 PCR test.[4] For 26 cases with SARS-CoV-2 serology, 73.1% (19/26) had a positive finding. 84.1% (53/63) were not vaccinated against SARS-CoV-2.

Several systematic reviews and meta-analyses of MIS-C or COVID-19 in children do not report the occurrence of abnormal liver findings or acute liver failure. While not understood for the pediatric population, investigators have reported SARS-CoV-2 liver tropism in adult patients with COVID-19.[45,46] It is important to note that most of the literature on MIS-C is based on cases that occurred prior to the emergence of the Delta variant.

- In PHO's *Pediatric Post-acute COVID-19 Syndrome (PACS) and Multisystem Inflammatory Syndrome in Children (MIS-C) – What We Know So Far*, that included 14 systematic reviews and four primary studies, did not identify acute hepatitis or jaundice in children with PACS or MIS-C; however, the focus of the rapid review was on signs and symptoms reported in at least 10% of cases (PHO 2022, forthcoming).[47] The date of the last literature search for this review was April 26, 2022.

- In a systematic review and meta-analyses of 123 studies and 4,475 children with MIS-C, Jiang et al. (2022) did not report liver failure in any of the patients, nor elevated liver enzymes or jaundice.[48] The date of the literature search was July 31, 2021 and the mean age of patients was 8.1 ± 2.37 years.

- In a systematic review and meta-analysis of 23 studies and 592 patients in Latin America and the Caribbean Region, Ruvinski et al. (2022) reported that no patients experienced acute hepatitis or had abnormal liver enzyme levels.[49] The date of the literature search was June 30, 2021 and the mean age of patients was 6.6 years (IQR: 6.0–7.4).

- Santos et al. (2021), in a systematic review and meta-analysis of 98 articles and 2,275 children, did not report any liver involvement in their included cases.[50] The date of the literature search was July 10, 2021 and the median age of children was 8.9 years.

While rare in pediatric cases of MIS-C and SARS-CoV-2 infection, there are reports of acute hepatitis and liver failure.

- In a nationwide (US) retrospective cohort study of 796,369 children with COVID-19 (≤10 years, mean age: 6.0 ± 3.1 years) and 550,694 children who contracted non-COVID-19 respiratory infections, Kendall at al. (2022) (preprint) reported that children with COVID-19 had a higher risk of elevated AST or ALT (hazard ratio [HR]: 2.5; 95% confidence interval [CI]: 2.03–3.12) and bilirubin (HR: 3.4, 95% CI: 2.16–5.18) at six months after infection.[51] Please note that elevated AST or ALT was defined as ≥100 U/L; elevated bilirubin was defined as ≥2 mg/dL.

- Nishiura et al. (2022) examined the association between the detection of at least one acute severe hepatitis case (meeting WHO case definition, Appendix A) among children and the cumulative number of Omicron VOC cases in 39 countries (illness onset from Oct 1, 2021 to Apr 27, 2022).[52] The authors noted that countries with a higher number of hepatitis cases in children tended to have a higher burden of Omicron infection (p=0.013). The authors hypothesize that prior exposure to Omicron may be associated with an increased risk of severe hepatitis among children. However, it is subject to confounding bias as the increase in Omicron infections generally occurred as restrictions eased, which would also increase the risk of other infections. The study included children ≤16 years. The study design has a number of limitations, and should be interpreted with caution.

- In a study of 47 children with previous COVID-19 in India, Rawat et al. (2022) (preprint) reported that 37 had hepatitis associated with COVID-19 (i.e., COVID-19 followed by acute hepatitis) while 10 had hepatitis associated with MIS-C (concurrent).[53] Children with hepatitis associated with COVID-19 had evidence of other infections and exposures (*Salmonella* sp., 21/37; dengue virus, 8/37; EBV, 8/37; human alphaherpesvirus 3 or varicella-zoster virus, 7/37; HAdV, 3/37); for MIS-C (HAV, 1/8). The mean age of children was 9 ± 3 years. Date of illness onset ranged from Apr to July 2021.

- In a systematic review and meta-analysis of 54 studies and 4,811 children with COVID-19 (543 with MIS-C), Kornitzer et al. (2021) reported that liver function tests were elevated in 0.6% (31/4,811) of children (for children with MIS-C there was one child with elevated liver function tests).[54] The authors did not report on acute hepatitis or other signs of liver damage (e.g., jaundice) among the included children. The authors did not report a mean or median age of included children. The date of the literature search for this systematic review was Mar 2021.

- In the US, Miller et al. (2022) reported on 4,470 children with MIS-C, in which 10.6% of children had signs of hepatomegaly/splenomegaly; however, the authors did not investigate hepatitis separately (symptom onset Feb 2020 to July 2021).[55] The authors did not report on liver transaminases or occurrence of jaundice. The median age of patients was 9 years (IQR: 5–13).

- In a study of 19 children with MIS-C and 70 children with non-MIS-C SARS-CoV-2 infection in Bulgaria (illness onset Oct 2020 to Feb 2021), Lazova et al. (2021) reported that 89.5% (17/19) of children with MIS-C had jaundice and one child required a liver transplant.[56] 15/70 of the non-MIS-C children had elevated AST and ALT, which was not significantly different from patients with MIS-C. In 7/11 children with MIS-C and with abdominal computerized tomography, there was evidence of an enlarged liver. The mean age of children with MIS-C was 9.5 ± 3.79 years.

- In a study of 65 children with MIS-C, in Chennai, India, Elilarasi et al. (2021) reported that five patients had evidence of acute liver failure.[57] The mean age of children was 5.7 ± 3.68 years and MIS-C onset ranged from July through Oct 2020.

- In a study of 44 children with MIS-C in New York, US (Apr to May 2020), Cantor et al. (2021) reported that 19 had hepatitis.[58] Eight of the 19 children with hepatitis had elevated ALT and patients with hepatitis had higher total bilirubin levels. In eight of the children with hepatitis, imaging revealed abnormal liver findings in five children.

- Antala et al. (2022) reported on severe hepatitis in four children with COVID-19, two with acute liver failure in the US.[59] The authors hypothesized that hepatitis in children with COVID-19 may be caused by complement activation and microangiopathy.

- Osborn et al. (2022) reported on a previously healthy 3-year-old child that developed PALF (date of illness onset not reported, prior to Apr 27, 2022).[60] After a mild infection with SARS-CoV-2, 3 weeks later the child developed PALF secondary to type 2 autoimmune hepatitis. The anti-LKM antibodies (1:1280) found in autoimmune hepatitis and the response to steroids was postulated to be consistent with MIS-C-like immunological injury driven by a superantigen from SARS-CoV-2. Laboratory results showed elevated ALT (939 U/L), AST (1,321 U/L), total bilirubin (5.5 mg/dL) and INR (2.0).

- Bonilla Gonzalez et al. (2022) reported on a 10-month old child with MIS-C that was associated with the development of acute liver failure and died (symptom onset Dec 2020).[61] The child tested positive for SARS-CoV-2 IgM and IgG, but negative by PCR. Upon admission, the child had elevated AST (1,459 U/L), ALT (2,049 U/L) and INR (2.0), with evidence of hepatocytes with multinucleated giant cell transformation.

- In a case report of a 5-month old with COVID-19 (date of illness onset not reported, prior to Apr 22, 2022), Ataollahi et al. (2022) reported that the child had gastrointestinal symptoms and jaundice, with hepatomegaly upon initial examination.[62] Upon admission to the ward, AST was 240 IU/L), ALT was 60 IU/L, total bilirubin was 41 mg/dL and INR was >7. The child developed hemophagocytic lymphohistiocytosis secondary to COVID-19 and later died.

- In a case report of a 10-month-old child that developed acute hepatitis, after presenting to an emergency department with a 2-day history of rhinitis, fever and cough (Brisca et al. 2021).[63] The child's mother had a SARS-CoV-2 infection 7 days earlier and child's NP swab was positive for SARS-CoV-2 upon PCR testing. Liver aminotransferases (AST: 860 U/L, ALT: 1,010 U/L) were elevated but returned to normal within a few days.

Given that the majority of studies included here were performed before the emergence of the Omicron variant (or even the Delta variant), there is a gap in our knowledge concerning novel symptoms or sequelae associated with recently emerged VOCs. While authors have hypothesized a possible link between Omicron emergence and hepatitis in children, further research is needed to test and/or confirm this hypothesis. Not all studies stated or used a standard cut-off for elevated liver enzymes or state how acute hepatitis is defined, or if acute hepatitis cases included here may be due to other causes. In addition, not all studies specify the timing of SARS-CoV-2 positivity in relation to hepatitis or elevation of liver enzymes.

Limitations

Current confirmed, probable and epi-linked case definitions of acute severe hepatitis of unknown etiology differ by country, with the UK, Scotland, US, Canada and WHO all using different case definitions based on the age of the case, reporting window, specifications and exclusions of other etiologies, and classification of cases as confirmed, probable/possible and epi-linked.[10] Case definitions are presented in Appendix A for comparison.

Testing for potential causative pathogens and investigation of potential etiologies for identified illness is at the discretion of the individual clinician,[10] although the UK advises that all cases admitted to hospital should be tested for SARS-CoV-2[10] and WHO advises that both infectious and non-infectious causes should be thoroughly investigated.[2] It is unclear whether there are true increases in cases of acute severe hepatitis in all jurisdictions investigating cases, as background rates are not available for all jurisdictions. In addition, liver biopsy, which can assist with determining etiology, may not be performed in less severe cases (i.e. cases without liver failure), further complicating the ability to draw definitive conclusions around etiology.

Anecdotal reporting has suggested that whole blood testing by PCR for adenovirus is more sensitive than PCR testing of plasma, and while European health authorities are attempting to conduct whole genome sequencing (WGS) of adenovirus, low levels of adenovirus in blood have complicated testing and have resulted in poor quality data.

Conclusions and Public Health Implications

Numerous cases of severe, acute hepatitis with an unknown etiology have been reported from several countries since Oct 2021. We expect additional reports of cases due to case finding activities in implicated countries that have adequate public health and clinical resourcing and capacity. Current case definitions have a focus on those with severe illness, so possibly do not capture individuals with milder illness presentations.

While investigators report detections of adenovirus in numerous cases, given the potential for persistent shedding of the virus and lack of pathology on liver biopsies consistent with direct viral damage (where performed), additional infectious and non-infectious causes continue to be explored, including SARS-CoV-2. To date in the UK (where the majority of cases have been identified), few epidemiological linkages have been identified among cases, including common food exposures, toxicants, animal exposure, travel, water source or parental occupation.[10]

Investigations into the etiology of acute severe hepatitis in children are ongoing. In addition, work is ongoing to look at background rates of acute severe hepatitis in many countries (including PHAC for Canada) to determine if the current number of cases is a true increase.

References

1. World Health Organization. Acute hepatitis of unknown aetiology – the United Kingdom of Great Britain and Northern Ireland [Internet]. Geneva: World Health Organization; 2022 [cited 2022 May 31]. Available from: https://www.who.int/emergencies/disease-outbreak-news/item/acute-hepatitis-of-unknown-aetiology---the-united-kingdom-of-great-britain-and-northern-ireland

2. World Health Organization. Multi-country–acute severe hepatitis in children of unknown etiology [Internet]. Geneva: World Health Organization; 2022 [cited 2022 May 31]. Available from: https://www.who.int/emergencies/disease-outbreak-news/item/multi-country-acute-severe-hepatitis-of-unknown-origin-in-children

3. Marsh K, Tayler R, Pollock L, Roy K, Lakha F, Ho A, et al. Investigation into cases of hepatitis of unknown aetiology among young children, Scotland, 1 January 2022 to 12 April 2022. Euro Surveill. 2022;27(15):2200318. Available from: https://doi.org/10.2807/1560-7917.ES.2022.27.15.2200318

4. World Health Organization. Acute hepatitis of unknown aetiology in children - multi-country [Internet]. Geneva: World Health Organization; 2022 [cited 2022 May 31]. Available from: https://www.who.int/emergencies/disease-outbreak-news/item/DON-389

5. Public Health Agency of Canada. Acute severe hepatitis in children [Internet]. Ottawa, ON: Government of Canada; 2022 [cited 2022 May 31]. Available from: https://www.canada.ca/en/public-health/services/diseases/acute-hepatitis-children.html

6. Baker JM, Buchfellner M, Britt W, Sanchez V, Potter JL, Ingram A, et al. Acute hepatitis and adenovirus infection among children — Alabama, October 2021–February 2022. MMWR Morb Mortal Wkly Rep. 2022;71:638-40. Available from: https://doi.org/10.15585/mmwr.mm7118e1

7. de Kleine RH, Lexmond WS, Buescher G, Sturm E, Kelly D, Lohse AW, et al. Severe acute hepatitis and acute liver failure of unknown origin in children: a questionnaire-based study within 34 paediatric liver centres in 22 European countries and Israel, April 2022. Euro Surveill. 2022;27(19):2200369. Available from: https://doi.org/10.2807/1560-7917.ES.2022.27.19.2200369

8. UK Health Security Agency. Investigation into acute hepatitis of unknown aetiology in children in England: technical briefing 3 [Internet]. London: Crown Copyright; 2022 [cited 2022 Jun 2]. Available from: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/1077027/acute-hepatitis-technical-briefing_3.pdf

9. Wadman M. Mysterious hepatitis outbreak sickens young children in Europe as CDC probes cases in Alabama. Science Insider [Internet], 2022 Apr 15 [cited 2022 May 31]; Europe. Available from: https://www.science.org/content/article/mysterious-hepatitis-outbreak-sickens-young-children-europe-cdc-probes-cases-alabama

10. van Beek J, Fraaij PL, Giaquinto C, Shingadia D, Horby P, Indolfi G, et al. Case numbers of acute hepatitis of unknown aetiology among children in 24 countries up to 18 April 2022 compared to the previous 5 years. Euro Surveill. 2022;27(19):2200370. Available from: https://doi.org/10.2807/1560-7917.es.2022.27.19.2200370

11. Squires JE, Alonso EM, Ibrahim SH, Kasper V, Kehar M, Martinez M, et al. North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition position paper on the diagnosis and management of pediatric acute liver failure. J Pediatr Gastroenterol Nutr. 2022;74(1):138-58. Available from: https://doi.org/10.1097/mpg.0000000000003268

12. Berardi G, Tuckfield L, DelVecchio MT, Aronoff S. Differential diagnosis of acute liver failure in children: a systematic review. Pediatr Gastroenterol Hepatol Nutr. 2020;23(6):501-10. Available from: https://doi.org/10.5223%2Fpghn.2020.23.6.501

13. Chapin CA, Burn T, Meijome T, Loomes KM, Melin-Aldana H, Kreiger PA, et al. Indeterminate pediatric acute liver failure is uniquely characterized by a CD103 CD8 T-cell infiltrate. Hepatology. 2018;68(3):1087-100. Available from: https://doi.org/10.1002/hep.29901

14. Chapin CA, Melin-Aldana H, Kreiger PA, Burn T, Neighbors K, Taylor SA, et al. Activated CD8 T-cell hepatitis in children with indeterminate acute liver failure: results from a multicenter cohort. J Pediatr Gastroenterol Nutr. 2020;71(6):713-9. Available from: https://doi.org/10.1097/mpg.0000000000002893

15. Ferrajolo C, Verhamme K, Trifirò G, t Jong GW, Giaquinto C, Picelli G, et al. Idiopathic acute liver injury in paediatric outpatients: incidence and signal detection in two European countries. Drug Saf. 2013;36(10):1007-16. Available from: https://doi.org/10.1007/s40264-013-0045-7

16. Kulkarni S, Perez C, Pichardo C, Castillo L, Gagnon M, Beck-Sague C, et al. Use of Pediatric Health Information System database to study the trends in the incidence, management, etiology, and outcomes due to pediatric acute liver failure in the United States from 2008 to 2013. Pediatr Transplant. 2015;19(8):888-95. Available from: https://doi.org/10.1111/petr.12596

17. Squires Jr RH, Shneider BL, Bucuvalas J, Alonso E, Sokol RJ, Narkewicz MR, et al. Acute liver failure in children: the first 348 patients in the pediatric acute liver failure study group. J Pediatr. 2006;148(5):652-8. Available from: https://doi.org/10.1016/j.jpeds.2005.12.051

18. Rajanayagam J, Coman D, Cartwright D, Lewindon PJ. Pediatric acute liver failure: etiology, outcomes, and the role of serial pediatric end-stage liver disease scores. Pediatr Transplant. 2013;17(4):362-8. Available from: https://doi.org/10.1111/petr.12083

19. Chiou FK, Logarajah V, Ho CWW, Goh LS, Karthik SV, Aw MM, et al. Demographics, aetiology and outcome of paediatric acute liver failure in Singapore. Singapore Med J. 2021 Oct 4 [Epub ahead of print]. Available from: https://doi.org/10.11622/smedj.2021138

20. Cheng Y, Xia Z, Huang C, Xu H. Case report: a novel cause of acute liver failure in children: a combination of human herpesvirus-6 infection and homozygous mutation in *NBAS* gene. J Clin Lab Anal. 2022;36(5):e24343. Available from: https://doi.org/10.1002/jcla.24343

21. Wollersheim SK, Humphries RM, Cherry JD, Krogstad P. Serological misdiagnosis of acute liver failure associated with echovirus 25 due to immunological similarities to hepatitis a virus and prozone effect. J Clin Microbiol. 2015;53(1):309-10. Available from: https://doi.org/10.1128/jcm.02724-14

22. Berzosa Sánchez A, de Ángeles Fernandez C, Callejas Caballero I, Illán Ramos M, Vecino López R, Bodas Pinedo A, et al. Acute hepatitis in an adolescent without travel history. Pediatr Infect Dis J. 2022;41(3):272-3. Available from: https://doi.org/10.1097/inf.0000000000003183

23. Silverio CE, Smithen-Romany CY, Hondal NI, Díaz HO, Castellanos MI, Sosa O. Acute liver failure in Cuban children. MED Rev. 2015;17:48-54. Available from: https://doi.org/10.37757/mr2015.v17.n1.10

24. Narkewicz MR, Horslen S, Belle SH, Rudnick DA, Ng VL, Rosenthal P, et al. Prevalence and significance of autoantibodies in children with acute liver failure. J Pediatr Gastroenterol Nutr. 2017;64(2):210-7. Available from: https://doi.org/10.1097%2FMPG.0000000000001363

25. Kainulainen L, Waris M, Söderlund-Venermo M, Allander T, Hedman K, Ruuskanen O. Hepatitis and human bocavirus primary infection in a child with T-cell deficiency. J Clin Microbiol. 2008;46(12):4104-5. Available from: https://doi.org/10.1128/jcm.01288-08

26. Islek A, Keskin H, Agın M, Aksungur N, Korkut E, Ozturk G. Parvovirus B19 infection as a rare cause of fulminant liver failure: a case report. Transplant Proc. 2019;51(4):1169-71. Available from: https://doi.org/10.1016/j.transproceed.2019.01.084

27. Leon LAA, Alves ADR, Garcia, RdCNC, Melgaço JG, de Paula VS, Pinto MA. Parvovirus B19 infection in a fatal case of acute liver failure. Pediatr Infect Dis J. 2017;36(12):e355-8. Available from: https://doi.org/10.1097/inf.0000000000001731

28. Whitworth JR, Mack CL, O'Connor JA, Narkewicz MR, Mengshol S, Sokol RJ. Acute hepatitis and liver failure associated with influenza A infection in children. J Pediatr Gastroenterol Nutr. 2006;43(4):536-8. Available from: https://doi.org/10.1097/01.mpg.0000232332.00677.3d

29. Yükselmiş U, Girit S, Çağ Y, Özçetin M. A child with acute liver failure associated with influenza A and resolved with plasma exchange treatment. Hong Kong J Emerg Med. 2018;25(5):281-5. Available from: https://doi.org/10.1177%2F1024907918754441

30. Grama A, Aldea C, Burac L, Delean D, Boghitoiu D, Bulata B, et al. Acute liver failure secondary to toxic exposure in children. Arch Med Sci. 2022;18(1):84. Available from: https://doi.org/10.5114%2Faoms.2019.87716

31. Vidal F, Sedan D, D'Agostino D, Cavalieri ML, Mullen E, Parot Varela MM, et al. Recreational exposure during algal bloom in Carrasco Beach, Uruguay: a liver failure case report. Toxins. 2017;9(9):267. Available from: https://doi.org/10.3390%2Ftoxins9090267

32. Government of Manitoba. Acute, severe hepatitis of unknown origin in children [Internet]. Winnipeg, MB: Government of Manitoba; 2022 [cited 2022 May 31]. Available from: https://www.gov.mb.ca/health/publichealth/diseases/acute_hepatitis.html

33. Lynch III JP, Kajon AE. Adenovirus: epidemiology, global spread of novel types, and approach to treatment. Semin Respir Crit Care Med. 2021;42(06):800-21. Available from: https://doi.org/10.1055/s-0041-1733802

34. European Centre for Disease Prevention and Control, World Health Organization Regional Office for Europe. Joint ECDC-WHO Regional Office for Europe hepatitis of unknown origin in children surveillance bulletin [Internet]. Geneva: European Centre for Disease Prevention and Control; 2022 [cited 2022 May 31]. Available from: https://cdn.ecdc.europa.eu/novhep-surveillance/

35. Brodin P, Arditi M. Severe acute hepatitis in children: investigate SARS-CoV-2 superantigens. Lancet Gastroenterol Hepatol. 2022 May 14 [Epub ahead of print]. Available from: https://doi.org/10.1016/s2468-1253(22)00166-2

36. Shieh W. Human adenovirus infections in pediatric population-an update on clinic-pathologic correlation. Biomed J. 2021;45(1):38-49. Available from: https://doi.org/10.1016/j.bj.2021.08.009

37. Huang D, Wang Z, Zhang G, Sai L. Molecular and epidemiological characterization of human adenoviruses infection among children with acute diarrhea in Shandong Province, China. Virol J. 2021;18(1):1-7. Available from: https://virologyj.biomedcentral.com/articles/10.1186/s12985-021-01666-1

38. Chandra P, Lo M, Mitra S, Banerjee A, Saha P, Okamoto K, et al. Genetic characterization and phylogenetic variations of human adenovirus-F strains circulating in eastern India during 2017–2020. J Med Virol. 2021;93(11):6180-90. Available from: https://doi.org/10.1002/jmv.27136

39. Liu M, Han Y, Sun J, Wei X, Zhao X, Wang B, et al. Comparison of the epidemiological and clinical characteristics of hospitalized children with pneumonia caused by SARS-CoV-2, influenza A, and human adenoviruses: a case-control study. Clin Pediatr. 2021;6(2):150-8. Available from: https://doi.org/10.1177%2F00099228211058601

40. Wang C, Liu J, Mi Y, Chen J, Bi J, Chen Y. Clinical features and epidemiological analysis of respiratory human adenovirus infection in hospitalized children: a cross-sectional study in Zhejiang. Virol J. 2021;18(1):1-11. Available from: https://doi.org/10.1186%2Fs12985-021-01705-x

41. Probst V, Rankin DA, Haddadin Z, Hamdan L, Rahman HK, Yanis A, et al. Adenovirus infection in hospitalized children with acute respiratory infection in Jordan. Pediatr Infect Dis J. 2022;41(4):277-83. Available from: https://doi.org/10.1097/inf.0000000000003423

42. Sakata H, Taketazu G, Nagaya K, Shirai M, Sugai R, Ikegami K, et al. Outbreak of severe infection due to adenovirus type 7 in a paediatric ward in Japan. J Hosp Infect. 1998;39(3):207-11. Available from: https://doi.org/10.1016/s0195-6701(98)90259-6

43. Özbay Hoşnut F, Canan O, Ozçay F, Bilezikçi B. Adenovirus infection as possible cause of acute liver failure in a healthy child: a case report. Turk J Gastroenterol. 2008;19(4):281-3. Available from: https://turkjgastroenterol.org/EN/adenovirus-infection-as-possible-cause-of-acute-liver-failure-in-a-healthy-child-a-case-report-133498

44. Matoq A, Salahuddin A. Acute hepatitis and pancytopenia in healthy infant with adenovirus. Case Rep Pediatr. 2016;2016:8648190. Available from: https://doi.org/10.1155%2F2016%2F8648190

45. Cai Q, Huang D, Yu H, Zhu Z, Xia Z, Su Y, et al. COVID-19: abnormal liver function tests. J Hepatol. 2020;73(3):566-74. Available from: https://doi.org/10.1016/j.jhep.2020.04.006

46. Bertolini A, van de Peppel, Ivo P., Bodewes FAJA, Moshage H, Fantin A, Farinati F, et al. Abnormal liver function tests in patients with COVID-19: relevance and potential pathogenesis. Hepatology. 2020;72(5):1864-72. Available from: https://doi.org/10.1002/hep.31480

47. Ontario Agency for Health Protection and Promotion (Public Health Ontario). Pediatric post-acute COVID-19 syndrome (PACS) and multisystem inflammatory syndrome in children (MIS-C) – what we know so far. Toronto, ON: Queen's Printer for Ontario; 2022 [Forthcoming].

48. Jiang L, Tang K, Irfan O, Li X, Zhang E, Bhutta Z. Epidemiology, clinical features, and outcomes of multisystem inflammatory syndrome in children (MIS-C) and adolescents—a live systematic review and meta-analysis. Curr Pediatr Rep. 2022;10(2):19-30. Available from: https://doi.org/10.1007%2Fs40124-022-00264-1

49. Ruvinsky S, Voto C, Roel M, Fustiñana A, Veliz N, Brizuela M, et al. Multisystem inflammatory syndrome temporally related to COVID-19 in children from Latin America and the Caribbean Region: a systematic review with a meta-analysis of data from regional surveillance systems. Front Pediatr. 2022;10:881765. Available from: https://doi.org/10.3389/fped.2022.881765

50. Santos MO, Gonçalves LC, Silva PA, Moreira AL, Ito CR, Peixoto FA, et al. Multisystem inflammatory syndrome (MIS-C): a systematic review and meta-analysis of clinical characteristics, treatment, and outcomes. J Pediatr (Rio J). 2021 Dec 3 [Epub ahead of print]. Available from: https://doi.org/10.1016/j.jped.2021.08.006

51. Kendall EK, Olaker VR, Kaelber DC, Xu R, Davis PB. Elevated liver enzymes and bilirubin following SARS-CoV-2 infection in children under 10. medRxiv 22274866 [Preprint]. 2022 May 14 [cited 2022 May 31]. Available from: https://www.medrxiv.org/content/10.1101/2022.05.10.22274866v1

52. Nishiura H, Jung S, Hayashi K. High population burden of Omicron variant (B.1.1.529) is associated with the emergence of severe hepatitis of unknown etiology in children. Int J Infect Dis. 2022 May 13 [Epub ahead of print]. Available from: https://doi.org/10.1016/j.ijid.2022.05.028

53. Rawat SK, Asati A, Jain A, Ratho RK. Covid-19 associated hepatitis in children (CACH) during the second wave of SARS-CoV-2 infections in Central India: is it a complication or transient phenomenon. medRxiv 21260716 [Preprint]. 2022 May 9 [cited 2022 May 31]. Available from: https://www.medrxiv.org/content/10.1101/2021.07.23.21260716v7

54. Kornitzer J, Johnson J, Yang M, Pecor KW, Cohen N, Jiang C, et al. A systematic review of characteristics associated with COVID-19 in children with typical presentation and with multisystem inflammatory syndrome. Int J Environ Res Public Health. 2021;18(16):8269. Available from: https://doi.org/10.3390%2Fijerph18168269

55. Miller AD, Zambrano LD, Yousaf AR, Abrams JY, Meng L, Wu MJ, et al. Multisystem inflammatory syndrome in children—United States, February 2020–July 2021. Clin Infect Dis. 2021 Dec 5 [Epub ahead of print]. Available from: https://doi.org/10.1093/cid/ciab1007

56. Lazova S, Alexandrova T, Gorelyova-Stefanova N, Atanasov K, Tzotcheva I, Velikova T. Liver involvement in children with COVID-19 and multisystem inflammatory syndrome: a single-center Bulgarian observational study. Microorganisms. 2021;9(9):1958. Available from: https://doi.org/10.3390/microorganisms9091958

57. Elilarasi S, Poovazhagi V, Kumaravel G, Srividya VG, Solomon J. Pediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2. Indian J Pediatr. 2021 Nov 24 [Epub ahead of print]. Available from: https://doi.org/10.1007/s12098-021-03954-8

58. Cantor A, Miller J, Zachariah P, DaSilva B, Margolis K, Martinez M. Acute hepatitis is a prominent presentation of the multisystem inflammatory syndrome in children: a single-center report. Hepatology. 2020;72(5):1522-7. Available from: https://doi.org/10.1002%2Fhep.31526

59. 59. Antala S, Diamond T, Kociolek LK, Shah AA, Chapin CA. Severe hepatitis in pediatric Coronavirus Disease 2019. J Pediatr Gastroenterol Nutr. 2022;74(5):631-5. Available from: https://doi.org/10.1097/mpg.0000000000003404

60. Osborn J, Szabo S, Peters AL. Pediatric acute liver failure due to type 2 autoimmune hepatitis associated with SARS-CoV-2 infection: a case report. JPGN Rep. 2022;3(2):e204. Available from: https://doi.org/10.1097%2FPG9.0000000000000204

61. Bonilla Gonzalez C, Hincapié Echeverría M, Plazas Pachón R, Mora Umaña P, Diaz Gómez BL, Gualdron Barreto N. Case report: fatal acute liver failure with giant cell transformation in a pediatric patient associated with MIS-C. Front Pediatr. 2021;9:1477. Available from: https://doi.org/10.3389%2Ffped.2021.780258

62. Ataollahi M, Haghshenas H, Karbasian F, Darban B, Haghighat M. Consider hemophagocytic lymphohistiocytosis as a new cause of death in COVID-19 with presentation of acute liver failure: a case report. Pediatr Infect Dis J. 2022;41(4):e186. Available from: https://doi.org/10.1097/inf.0000000000003487

63. Brisca G, Mallamaci M, Tardini G, Martino L, Chianucci B, Ricci M, et al. SARS-CoV-2 infection may present as acute hepatitis in children. Pediatr Infect Dis J. 2021;40(5):e214-5. Available from: https://doi.org/10.1097/inf.0000000000003098

64. Ministry of Health. Acute hepatitis [Internet]. Toronto, ON: Queen's Printer for Ontario; 2022 May 20 [cited 2022 May 31]. Available from: https://www.health.gov.on.ca/en/pro/programs/publichealth/acute_hepatitis/default.aspx

65. Centers for Disease Control and Prevention. Recommendations for adenovirus testing and reporting of children with acute hepatitis of unknown etiology [Internet]. Atlanta, GA: Centers for Disease Control and Prevention; 2022 [cited 2022 May 31]. Available from: https://emergency.cdc.gov/han/2022/han00462.asp

Appendix A. Confirmed, probable/possible and epi-linked case definitions for acute severe hepatitis of unknown origin among young children

Jurisdiction or Organization (Date last updated)	Confirmed	Probable/Possible	Epi-linked
World Health Organization(WHO)[4] (May 27, 2022)	NA	A person presenting with an acute hepatitis (non hepatitis virus A-E[1,2]) with serum ALT or AST > 500 IU/L, who is ≤16 years, since Oct 1, 2021	A person presenting with an acute hepatitis (non hepatitis virus A-E[1,2]) of any age who is a close contact of a probable case, since Oct 1, 2021.
European Centre for Disease Prevention and Control (ECDC)[34] (May 19, 2022)	NA	A person presenting with an acute hepatitis (non hepatitis virus A-E[3]) with serum ALT or AST > 500 IU/L, who is ≤16 years, since Oct 1, 2021	A person presenting with an acute hepatitis (non hepatitis virus A-E[3]) of any age who is a close contact of a probable case, since Oct 1, 2021.
England, Wales, Northern Ireland[8] (May 19, 2022)	A person presenting with an acute hepatitis (not due to hepatitis virus A-E[1], metabolic disorder, inherited or genetic condition, congenital/ mechanical cause) with serum ALT or AST > 500 IU/L, who is ≤10 years, since Jan 1 2022.	A person presenting with an acute hepatitis (not due to hepatitis virus A-E[1], metabolic disorder, inherited or genetic condition, or congenital/mechanical cause) with ALT or AST > 500 IU/L, who is 11 to 16 years old, since Jan 1 2022.	A person presenting with an acute hepatitis ((not due to hepatitis virus A-E[1], metabolic disorder, inherited or genetic condition, congenital/ mechanical cause) of any age who is a close contact of a confirmed case, since Jan 1 2022.

Jurisdiction or Organization (Date last updated)	Confirmed	Probable/Possible	Epi-linked
Scotland[8] (May 19, 2022)	A person presenting with a serum ALT or AST > 500 IU/L without any known cause (not due to hepatitis virus A-E[1], CMV or EBV), who is 10 years of age and under or a contact of any age of a possible or confirmed case, since Jan 1, 2022.	A person presenting with jaundice without any known cause (not due to hepatitis virus A-E[1], CMV or EBV), who is ≤10 years or contact of any age to a possible or confirmed case, since Jan 1, 2022.	NA
Canada - Public Health Agency of Canada (PHAC)[32] (May 13, 2022)	NA	A person who is 16 years and younger presenting with severe acute hepatitis since Oct 1, 2021 and requiring hospitalization, AND with elevated serum ALT or AST > 500 IU/L, AND excluding hepatitis caused or attributed to a hepatitis virus (A, B, C, D, E[4]) or a known or expected presentation of a drug or medication; a genetic, congenital, or metabolic condition; an oncologic, vascular, or ischemia related condition; or an acute worsening of chronic hepatitis.	NA
Ontario Ministry of Health[64] (May 20, 2022)	NA	A person who is 16 years and younger presenting with clinical evidence of severe acute hepatitis since Oct 2021 and requiring hospitalization, AND with elevated serum ALT/AST > 500 IU/L or INR > 2.0, AND excluding hepatitis caused or attributed to a hepatitis virus (A, B, C, D, E[4]) or a known or expected presentation of a drug or medication; a genetic, congenital, or metabolic condition; an oncologic, vascular, or ischemia related condition; or an acute worsening of chronic hepatitis.	NA

Jurisdiction or Organization (Date last updated)	Confirmed	Probable/Possible	Epi-linked
United States Centers for Disease Control and Prevention (CDC)[65] (Apr 21, 2022)	NA	Children <10 years of age with elevated ALT or AST (>500 U/L) who have an unknown etiology for their hepatitis (with or without any adenovirus testing results, independent of the results) since Oct 1, 2021	NA

Abbreviations: NA, not applicable; AST, aspartate transaminase; ALT, alanine transaminase; CMV, cytomegalovirus; EBV, Epstein-Barr virus

[1]If hepatitis virus A-E serology results are awaited, but other criteria met, these are classified as 'pending classification'

[2]Cases with other explanations for their clinical presentation are discarded.

[3] Cases of hepatitis with known aetiology such those due to specific infectious diseases, drug toxicity, and metabolic hereditary, or autoimmune disorders should not be reported under this protocol.

[4]If hepatitis virus D or E serology results are pending or test was not done, but other criteria met, these can be reported as probable cases.

Citation

Ontario Agency for Health Protection and Promotion (Public Health Ontario). Acute severe hepatitis of unknown origin among young children – what we know so far. Toronto, ON: Queen's Printer for Ontario; 2022.

Disclaimer

This document was developed by Public Health Ontario (PHO). PHO provides scientific and technical advice to Ontario's government, public health organizations and health care providers. PHO's work is guided by the current best available evidence at the time of publication. The application and use of this document is the responsibility of the user. PHO assumes no liability resulting from any such application or use. This document may be reproduced without permission for non-commercial purposes only and provided that appropriate credit is given to PHO. No changes and/or modifications may be made to this document without express written permission from PHO.

Public Health Ontario

Public Health Ontario is an agency of the Government of Ontario dedicated to protecting and promoting the health of all Ontarians and reducing inequities in health. Public Health Ontario links public health practitioners, front-line health workers and researchers to the best scientific intelligence and knowledge from around the world.

For more information about PHO, visit publichealthontario.ca.

Ontario